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(57) Abstract

The present invention relates to a pharmaceutical composition comprising as active ingredient a compound selected among somatostatin or one of its analogs, diazoxide or one of its analogs, cyclothiazide or one of its analogs and metformin, for the treatment of syndrome X of Reaven (also called "Hyper Insulinemia syndrome" or "The Deadly Quartet").

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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SYNDROM X OF REAVEN

The present invention relates to a pharmaceutical composition comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazideor one of its analogs(as herein defined) and metformin, for the treatment of syndrome X of Reaven (also called "Hyper Insulinemia syndrome" or "The Deadly Quartet").

Somatostatin and its analogs, e.g. octreotide, are known for the treatment of the reduction of the secretion of Insulin caused by insulimonas. Moreover, they are known for the treatment of certain tumors, gastrointestinal diseases, etc. However, their effectivity for the reduction of the resistance to insulin has so far not been known.

It is also known that Diazoxide, Cyclothiazide and Metformin achieve the reduction of the resistance to Insulin. Moreover, it is known that Metformin is used in the treatment of Diabetes and reduces risk factors in carbovascular diseases in NIDDM.

Diazoxide, Cyclothiazide and Metformin have the following formulae:

a. Diazoxide: 7-chloro-3-methyl-24-1,2,4-benzothiodiazine 1,1-dioxide.

b. Cyclothiazide: 3-bicyclo[2.2.1]hept-5-en-2yl-6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

c. Metformin: N,N-Dimethylimidodicarbonimide diamide.

However, those compounds have so far not been known for the treatment of the risk factors of syndrome X of Reaven.

Syndrome X includes, inter alia, the following risk factors: a. excessive blood pressure; b. dislipidemia, i.e. increase of th amount of Triglycerides in the blood, reduction of the amount of HDL and increase of the amount of LDL, c. excessive blood

coagulation due to Plasminogen Activator Inhibitor-1 (PAI-1) increased in the blood; d. central obesity; e. Glucose intolerances - from ocult Diabetes to overt Diabetes f. increase of Insulin in the blood, i.e. the pancreas secretes more Insulin in order to overcome high Insulin resistance.

All the risk fators of syndrome X of Reaven are, inter alia, caused by a high resistance to Insulin. Thus, apparently said symptoms could be treated simultaneously if there would be a reduction to the resistance to Insulin.

Said risk factors either separately but mostly in combination are decisive factors in the appearance of Ischemic Heart disease, e.g. Angina Pectoris, Myocard Infarct; Cerebral Vascular Diseases and the like.

Until now, all said risk factors had to be treated separately as there was no pharmaceutical composition which could treat simultaneously all of them. However, said separate treatments are not always effective as very often the treatment of one risk factor severes the condition of another risk factor. It has therefore been desirable to find a pharmaceutical composition which can treat simultaneously all the various risk factors which are included in syndrome X of Reaven.

We have now found that due to the fact that the reduction of the resistance to Insulin can be achieved by administering a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs(as herein defined) and metformin, said treatment may enable the treatment of all risk factors of syndrome X of Reaven simultaneously.

The present invention thus consists in pharmaceutical preparations for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazideor one of its analogs(as herein defined) and metformin.

The present invention also comprises the use of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined),

cyclothiazideor one of its analogs (as herein defined) and metformin in the preparation of a pharmaceutical preparation for th treatment of the risk factors of syndrome X of Reaven.

Analogs of somastostatin in connection with the present invention mean any analog compound of somatostatin which biologically activate one or more somastostatin receptors. Said receptors cause the reduction of the resistance to Insulin and thus enable the combined treatment of all risk factors of syndrom X of Reaven and are thus effective in primarily & secondary preventing and/or treating Ischemic Heart disease, such as, Angina Pectoris, Myocard Infarcts ; Cerebral Vascular Diseases, etc.

As receptors there should be mentioned, inter alia, the following human somatostatin receptors, which are described in Steven W.J. Lamberts, et al. 1996. Octreotide.. The New England Journal Med. Jan. 25. pp. 246-54. These receptors are:

1. hSSTR1
   Present in the brain, lung, stomach, jejunum, kidneys, liver and pancreas. It is located on chromosom 14q13. It has 391 amino acids and its formula is given in Yamada et. al., Biochemical and Biophysical Research Communications, 1993, Vol. 195, No. 2., pages 844-852.
2. hSSTR2
   Present in the brain and in the kidneys, It is located on chromosom 17q24. It has 369 amiono acids and its formula is given in Yamada.
3. hSSTR3
   Present in the brain and in the pancreas. It is located on chromosome 22q13.1. It has 418 amino acids and its formula is given in Yamada.
4. hSSTR4
   Present in the brain and in the lung. It is located on chromosome 20. It has 388 amino acids and its molecular weight is 41,867. Its formula is given in Yamada.
5. hSSTR4
   Present in the brain, heart, adrenal glands, placenta, pituitary, small intestines and skeletal muscles. It is located on chromosome 20p11.2. It has 364 amino acids,

its molecular weight is 39,176 and its formula is given in Yamada.

All receiptors have common features:

1. They have a similarity in the configuration in the seven areas which do extend out of the membrane TM1....TM7)
2. Asp-Arg-Tyr at the end of the NH -terminal of the second loop which is in the cell.
3. Aspartic acid (Asp) is located in the third loop outside the cell.

The receptors which are especially important in reducing the Insulin resistance are receptors 2 and 5, also but less receptor 3. Receptors 1 and 4 are less important in this respect.

The use of somatostatin is not always satisfactory as it is effective only for a short time. Therefore the use of Octreoide, the most known analog of somatostatin or of another long acting Somatostatin, is preferred.

The analogs of somastostatin should comprise the chain D-Trp-Lys. Said chain constitute the critical core of the active analogs and is essential for the activation of the receptors.

Most analogs comprise the chain Phe-D-Trp-Lys.

Many analogs comprise the chain Phe-D-Trp-Lys-Thr being present in positions 7 - 10 of Somatostatin 14.

Suitable analogs of somatostatin being part of the pharmaceutical composition according to the present invention are, for example,:

1. Octreotide.
2. Vapreotide.
3. Lanreotide.
4. Cyclopeptide somatostatin analogues selected among :

Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-δ-aminobutyric-Phe]
Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]

Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a)
Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]
Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser] (Ahep =(b)
Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]
Cyclo[Ahep-Phe-D-Trp-Lys-Thr]
Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]
Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)] (Ahex = (c)
Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)] (Aoct = (d)
Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]

(a) Bzl = benzyl
(b) Ahep = 7-aminoheptanoyl
(c) Ahex = 6-aminohexanoyl
(d) Aoct = 8-amino-octanoyl;

5. D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol
6. D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH_2 (Nal = (1)
7. D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH_2
8. D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH_2
9. D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH_2 (Abu = (2)
10. D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH_2
11. D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH_2
12. c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3)
13. D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2 (Cpa = (4)
14. D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2
15. D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2
16. D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2
17. D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH_2
18. D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH_2
19. D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2
20. D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2
21. D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH_2

(1) Nal L-3(2-naphthyl)alanine
(2) Abu L-α-amino-n-butyric acid
(3) Ahep 7,aminoheptanoic acid
(4) Cpa L-p-chlorophenylalanine

22. Polypeptides of the formula:

X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y

wherein A is L- or D-Trp,

X is H-$(Aeg)_m$-Cys- or H-$(Aeg)_m$-Ala-Gly-Cys-,

Y is -Cys-$(Aeg)_n$-OH or

X and Y taken together are a 2-aminoethyl-glycyl group in the ring position and

m and n are 0, 1, 2, provided that

m and n are at least 1,

and their cyclic disulfide derivatives.

23. A peptide of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH

3 4 5 6 7 8 9 10 11 12 13 14

in which

Bmp represents the desaminocysteine radical,

X represents Asn,

trp represents D-Trp that may be substituted in the benzene ring by a halogen atom, and

Y represents the radical of an alpha-(lower alkyl)amino-(lower alkyl)-carboxylic acid having a minimum of 4 and a maximum of 8 carbon atoms, in which the two lower alkyl radicals can be connected to one another witha single C-C bond, an oxygen atom or a sulphur (II) atom.

24. Cyclic octapeptides of the formula

Asn-Phe-Phe-Trp-Lys-Thr-Phe-Gaba(Ar)

5 6 7 8 9 10 11 12

in which

Trp represents L-Trp or D-Trp, in which the benzene ring may be substituted by a fluorine atom, and

Gaba(Ar) represents the residue of a -aminobutyric acid substituted by a cyclic hydrocarbyl radical Ar selected from the group consisting of cyclohexyl; phenyl optionally substituted by halogen, nitro or phenoxy; and naphthyl

optionally substituted by halogen.

25. A compound of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R_8

-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R_{18}-R_{19}-Phe-Phe-D

-Trp-Lys-Thr-R_{25}-R_{26}-R_{27}-R_{28}-OH wherein R_8 is

Met or Leu, R_{19} is Lys or des R_{18}, R_{19} is Asn or

des R_{19}, R_{25} is Phe or Tyr, R_{26} is Thr or des

R_{26}, R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys.

26. A compound of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R_8-Ala-Pro

-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R_{18}-R_{19}-Phe-Phe-D-Trp-Lys

-Thr-R_{25}-R_{26}-R_{27}-R_{28}-OH wherein R_8 is Met or

Leu, R_{18} is Lys or des R_{18}, R_{19} is Asn or des

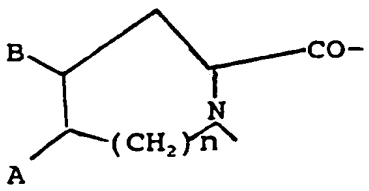
R_{19}, R_{25} is Phe or Tyr, R_{26} is Thr or des R_{26},

R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

27. A cyclic hexapeptide of the formula

-X - Phe-D-Trp-Lys-Y-Phe-

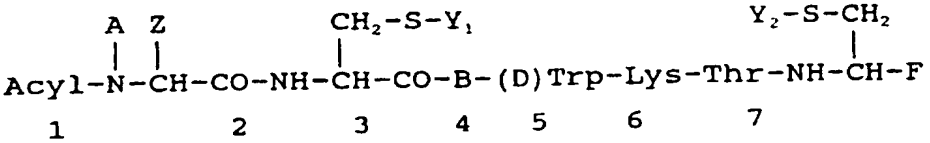
in which X represents the radical of an L-aminoacid of the formula



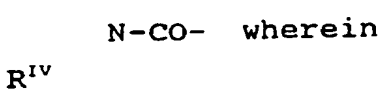
in which A and B are identical or different and denote alkyl

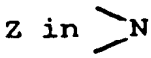
having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms,
n denotes 0 or 1, and
Y represents an aliphatic or aromatic L-aminoacid the side-chair of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

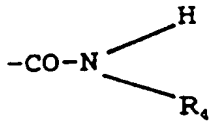
28. An N-acyl-polypeptide of formula,



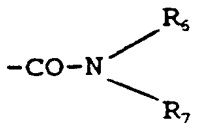
wherein
"Acyl" is a group of formula $R^{I}CO-$ wherein R^{I} is C_{1-20} alkyl or phenyl; a group of formula $R^{II}SO_2-$ wherein R^{II} is C_{1-20}-alkyl, phenyl or tolyl; a group



R^{III} and R^{IV} are each independently hydrogen or C_{1-10}alkyl; or biotinyl,
A is hydrogen or C_{1-3}alkyl,
>N-CH(Z)-CO- is an (L)- or (D)-phenylalanine residue optionally ring-substituted by NO_2, or an (L) or (D)-norleucine residue,
whereby
Z in  -CO- represents the remainder of said residue,
B is -Phe- optionally ring-substituted by NO_2,
F is a group of formula



wherein R_4 is hydrogen or a group of formula
$-CH(R_5)-X$,
R_5 is $CH_3CH(OH)-$, i-butyl or benzyl
X is a group of formula $-COOR_1$,
$-CH_2OR_2$ or



wherein R_1, R_6 and R_7 are each hydrogen or C_{1-3}alkyl, and

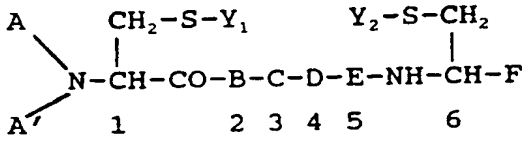
R_2 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

the group $-CH(R_5)-X$ having the (D)- or (L)-configuration, and

Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each indepen-dently have the (L)- or (D)-configuration, and with the proviso that:

i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only.

29. A polypeptide of the formula



wherein

A is C_{1-12}alkyl, C_{7-10}phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C_{1-11}alkyl, phenyl or C_{7-10}phenylalkyl, or

ii) RCO- is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or C_{1-3}alkyl,

b) H-Asn-, or

c) H-Nle-Asn-,

the α-amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di-C_{1-12}alkylated,

A′ is hydrogen or, when A is C_{1-12}alkyl or C_{7-10}phenylalkyl, also C_{1-12}alkyl or C_{7-10}phenylalkyl,

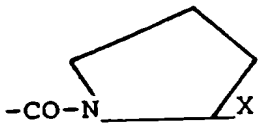
B is -Phe-optionally ring-substituted by halogen and/or C_{1-3}alkyl,

C is -(L)- or -(D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen and/or C_{1-3}alkyl,

D is -Lys- optionally α-N-methylated and optionally Σ-N-C_{1-3}-alkylated,

E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally α-N-methylated,

F is a group of formula $-COOR_1$, $-CH_2OR_2$, $-CO-N(R_3)(R_4)$ or



wherein R_1 is hydrogen or C_{1-3}alkyl,

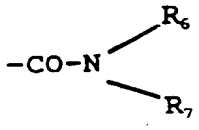
R_2 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R_3 is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}-phenylalkyl,

R_4 is hydrogen, C_{1-3}alkyl or, when R_3 is hydrogen or methyl, also a group of formula $-CH(R_5)-X$,

R_5 is hydrogen, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, $-CH_2-OH$, $-CH(CH_3)-OH$, isobutyl or benzyl

X is a group of formula $-COOR_1$, $-CH_2OR_2$ or



wherein

R_1 and R_2 have the meanings given above,

R_6 is hydrogen or C_{1-3}alkyl and

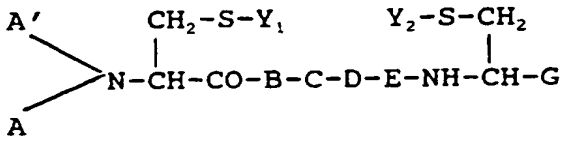
R_7 is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenylalkyl,

the group $-CH(R_5)-X$ having the D- or L- configuration, and

Y_1 and Y_2 are each hydrogen or together represent a direct

bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

30. A compound of formula



wherein

A is C_{1-12}alkyl, C_{7-10}phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C_{1-11}alkyl, phenyl or C_{7-10}phenylalkyl or

ii) RCO- is

a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, No_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy;

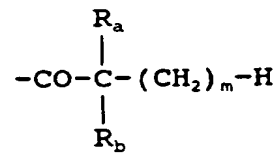
b) the residue of a natural or synthetic α-a-mino acid other than defined under a) above or of a corresponding D-amino acid, or

c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

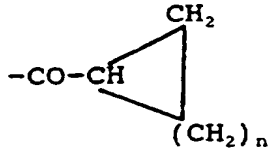
C_{1-8}alkanoyl,

A' is hydrogen,

Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of formulae (1) to (5).



(1)



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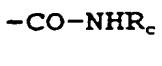

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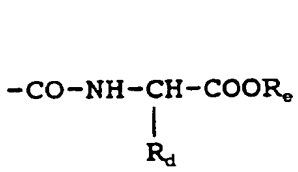

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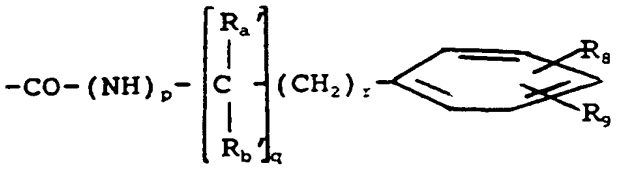


(5)

wherein

R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is (C_{1-6})alkyl

R_d represents the substituent attached to the α-carbon atom of a natural or synthetic α-amino acid (including hydrogen)

R_e is (C_{1-5})alkyl

R_a' and R_b' are independently hydrogen, methyl or ethyl,

R_8 and R_9 are independently hydrogen, halogen, (C_{1-3})alkyl or (C_{1-3})alkoxy,

P is 0 or 1,

q is 0 or 1, and

r is 0, 1 or 2,

B is -Phe- optionally ring-substituted by halogen, NO_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy (including pentafluoroalanine), or ß-naphthyl-Ala

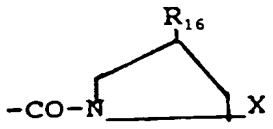
C is (L)-Trp- or (d)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, NO_2, NH_2 OH, C_{1-3}alkyl and/or C_{1-3} alkoxy,

D is Lys, Lys in which the side chain contains O or S in ß-position, ∮F-Lys or δF-Lys, optionally α-N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly. residue

E is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue

G is a group of formula

$-COOR_7$, $-CH_2OR_{10}$, $-CON(R_{11})(R_{12})$ or



wherein

R_7 is hydrogen or C_{1-3}alkyl,

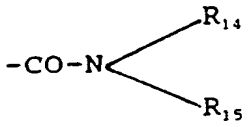
R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R_{11} is hydrogen, C_{1-9}alkyl, phenyl or C_{7-10}phenyl-alkyl,

R_{12} is hydrogen, C_{1-3}alkyl or a group of formula $-CH(R_{13})-X_1$,

R_{13} is CH_2OH, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, or $-CH(CH_3)OH$ or represents the substituent attached to the α-carbon atom of a natural or synthetic α-amino acid (including hydrogen) and

X_1 is a group of formula $-COOR_7$, $-CH_2OR_{10}$ or



wherein

R_7 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-3}alkyl and

R_{15} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenylalkyl, and

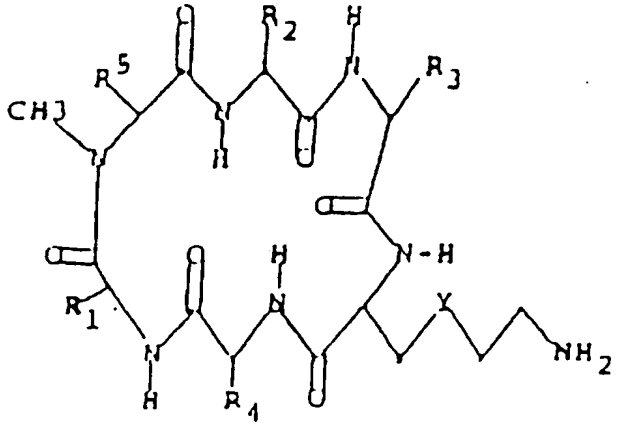
R_{16} is hydrogen or hydroxy,

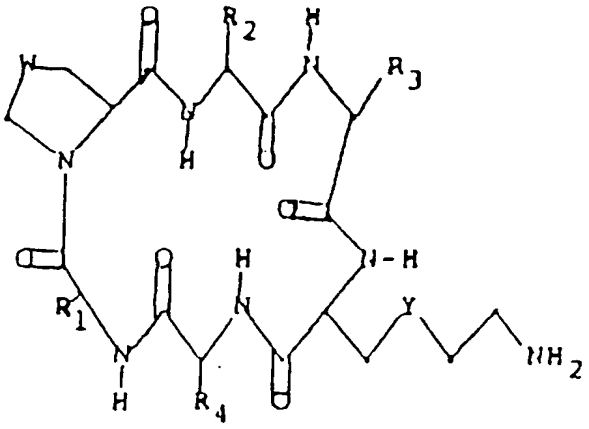
with the proviso that

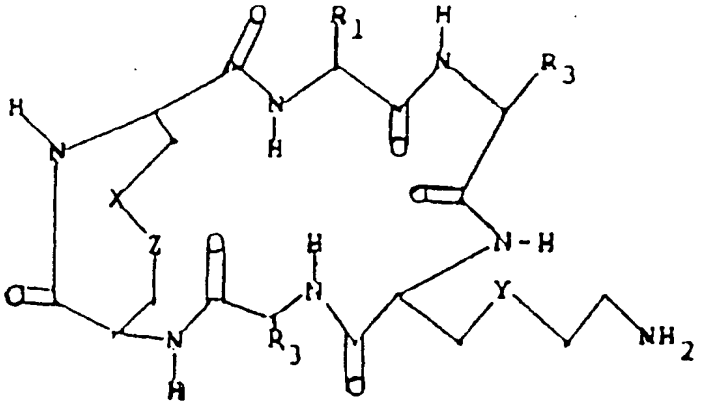
when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2-and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)- configuration.

31. A somatostatin analog selected from the compounds of the following formulae







wherein

W is S or $(CH_2)_s$ where s is 0, 1 or 2;

one of X and Z is S and the other is S or CH_2;

Y is S or $(CH_2)_t$ where t is 0, 1 or 2;

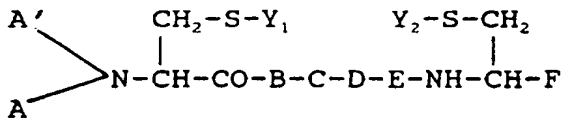
each of R_1 and R_2 independently of the other, is C_{1-5} alkyl, benzyl, benzyl having one or two C_{1-5} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-5} alkoxy substituents, or C_{1-5} alkyl substituted with 5- or 6-membered heterocyclic ring;

R_3 is 3-indolymethyl, either unsubstituted or having C_{1-5} alkyl, C_{1-5} alkoxy or halogen substitution;

R_4 C_{1-5} alkyl, C_{1-5} hydroxyalkyl, benzyl, carboxy-(C_{1-5} alkyl), amino (C_{1-5} alkyl) or benzyl having a C_{1-5} alkyl, halogen, hydroxy, amino, nitro and/or C_{1-5} alkoxy substituent;

R_5 is C_{1-5} alkyl, benzyl, or benzyl having a C_{1-5} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-5} alkoxy substituent,

compounds of Formula



wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl, or

ii) RCO-is

a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2, NH_2, OH, C_{1-3} alkyl and/or C_{1-3} alkoxy

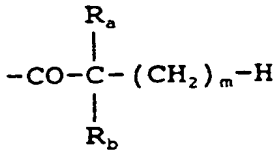
b) the residue of a natural α-amino acid other than defined under a) above or of a corresponding D-amino acid, or

c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above, the α-amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di-C_{1-12} alkylated,

A′ is hydrogen or, when A is C_{1-12} alkyl or C_{7-10} phenylalk- also C_{1-12} alkyl or C_{7-10} phenylalkyl,

Y_1 and Y_2 represent together a direct bond or

each of Y_1 and Y_2 is independently hydrogen or a radical of the formulae



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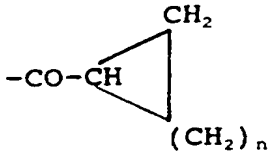

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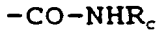

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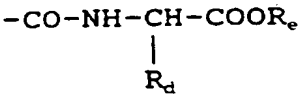

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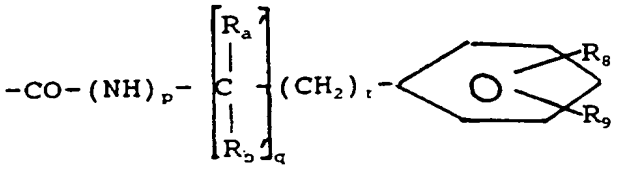


(5)

wherein R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is (C_{1-6})alkyl

R_d represents the substituent attached to the α-carbon atom of a natural α-amino acid (including hydrogen)

R_e is (C_{1-5})alkyl

R_a' and R_b' are independently hydrogen, methyl or ethyl,

R_8 and R_9 are independently hydrogen, halogen, (C_{1-3})alkyl or (C_{1-3})alkoxy,

p is 0 or 1,

q is 0 or 1, and

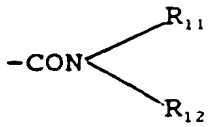
r is 0, 1 or 2,

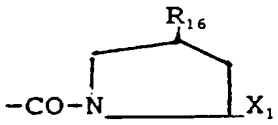
B is -Phe- optionally ring-substituted by halogen, No_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy, or naphthylalanine.

C is (L)-Trp- or (D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, No_2, NH_2, OH, C_{1-3} alkyl and/or C_{1-3} alkoxy,

D is -Lys-, ThiaLys, F-Lys, δF-Lys or Orn, optionally α-N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,

E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue

F is a group of formula $-COOR_7$, $-CH_2OR_{10}$,  or



wherein R_7 is hydrogen or C_{1-3}alkyl,

R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

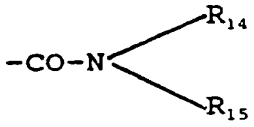
R_{11} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}-phenylalkyl,

R_{12} is hydrogen, C_{1-3}alkyl or a group of formula $-CH(R_{13})-X_1$,

R_{13} is CH_2OH, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, or $-CH(CH_3)OH$ or

represents the substituent attached to the α-carbon atom of anatural α-amino acid (including hydrogen) and

X_1 is a group of formula $-COOR_7$, $-CH_2OR_{10}$ or



wherein

R_7 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-3}alkyl and

R_{15} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenylalkyl, and

R_{16} is hydrogen or hydroxy,

with the proviso that

when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)-configuration

and compounds of the following formulae

H-Cys-Phe-(D)Trp-Lys-Thr-Phe-Cys-OH

Asn-Phe-Phe-(D)Trp-Lys-Thr-Phe-Gaba

-MeAla-Tyr-(D)Trp-Lys-Val-Ph

NMe-Phe-His-(D)Trp-Lys-Val-Ala.

32. Somatostatin analogs

X-Cys-D-o-Trp-E-F-Cys-Y I

X-Cys-Lys-Asn-Phe-D-o-Trp-E-F-Phe-Thr-Ser-Cys-Y II

I,II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R^1); R^1 = C_{1-8}(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH_2, NHR^1.

33. Peptides $RR^1NCHR^2CONHCH(CH_2SR^4)CO$-Phe-Trp-Lys-X-$NHCHR^3CH_2SR^5$ [R = inorg. or org. acyl group, R^1 = H, alkyl, $NCHR^2CO$ moiety = I.

$Me(CH_2)_8CO$-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol I

or D-Phe (optionally ring substituted by halo, NO_2, OH, alkyl. alkoxy); Phe, Trp, (D or L) ,may be ring substituted by NO_2, NH_2, OH, alkyl, alkoxy; Lys may be α-N-methylated and Σ-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R^3 = CO_2H, CH_2OH, carbamoyl, R^4 = R^5 = H, R^4R^5 = bond]

34. H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-X^1-x^2-Phe-Phe-D-Trp-Lys-Tys-Thr-X^3-X^4-X^5-X^6-OH

35. H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

Said compounds (34 and 35) appear in Chemical Abstracts 98, 1983 1 43839 q

36. c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

a) R,S-δ-Bn-o-AMPA

b) R-α-Bn-NMe-o-AMPA

c) Phe-Pro

Said cmpounds and similar ones appear in Brecx et al., Lett. Pept. Sci.1995, 2 (3/4): 165-8 , "Somatostatin analogs contai- ning 0-amino methyl phenyl acetic acid as a bridge unit"; and Tourwe, Lett. Pept. Sci. 1995, 2 (3/4): 182-6, "Conformation directed design of cyclic Somatostatin containing a BVI-turn mimetic".

37. H_2N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

38. H_2N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

39. D-ß-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

40. Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2

41. D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH_2

42. D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2

43. D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

44. D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2

45. 3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

46. c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)

Aha = 7 -amino heptanoic acid.

Analogs of Diazoxide and Cyclothiazide are compounds which affect the receptor being adenosine 5'- triphosphate sensitive K^+ channels.

Suitable analogs of Diazoxide and of Cyclothiazide are indicated, for example, in a paper of Bertolino et al., appearing in Receptor-Channels 1993 1(4):267-78 "Modulation of AMPA/Kainate Receptors by Analogs of diazoxide and cyclothiazide in thin

slices of rat hippocampus". However, the analogs which may be used in the pharmaceutical composition according to the present invention are not restricted to the analogs given in said paper and any other analog having the proper properties may be used.

The pharmaceutical preparation according to the present invention may also comprise additional compounds such as compounds having an additional pharmaceutical effect, carriers, solvents, emulgamators, etc.

In view of the fact that diazoxide sometimes has undesired salt and water retention, which may be relieved by certain thiazide diuretics, e.g. 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Chlorothiazide); 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Hydrochlorthiazide); 6-chloro-3-(dichloromethyl)-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Trichlormethiazide); or 6-chloro-3,4-di-hydro-2-methyl-3[(2,2,2-trifluoroethyl)thiomethyl]-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (Polythiazide), the pharmaceutical compositions according to the present invention may comprise, in addition to Diazoxide and/or one of its analogs, as an additional compound having a pharmaceutical effect, one or more of the above thiazides or a thiazide having similar properties. Said thiazide diuretics may prevent the salt and water retention.

The present invention also comprises a method for the treatment of the risk factors of syndrome X of Reaven by applying to a patient a pharmaceutically effective dosage of a pharmaceutical preparation according to the present invention comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs(as herein defined) and metformin.

Said dosage should preferably not exceed 50μg/kg/day of the active ingredient (calculated on Octreotide), preferably not exceeding 40μ/kg/day. Said dosage is given in any suitable manner. It may be given as one portion once a day or even in two days or more when given in slow release form, or being divided into 3-4 dosages which are applied in equal periods of time for Octreotide, or 1 - 2 times a day for analogs with a higher $t_{\frac{1}{2}}$.

Said dosage should preferably not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and preferably not exceed 15/mg/day in the treatment of children. The amount of Metformin applied should preferably not exceed 2.5 g/day divided into 2 - 3 portions.

Should any of the above thiazide diuretics be added the added amounts are, for example, the following:

Chlorothiazide: 500 - 2000 mg a day;
Hydrochlorothiazide: 50 - 200 mg a day;
Trichloromethiazide: 12.5 - 50 mg a day;
Polythiazide: 1- 4 mg a day.

Said dosage has to be re-calculated on the basis of the analog being the active ingredient. Moreover, the exact dosages have to be adapted to the condition of the patients and to its specific properties e.g. weight, age, etc.

The composition may be administered in various manners. This depends in particular on the analog being the active ingredient. Thus octreotide is advantageously injected sub-cutaneously as a saline solution. Cyclo(N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe) is advantageously administered per os.

The treatment is performed, as indicated above, against the risk factors of syndrome X of Reaven, in particular against the following diseases in order to primarily and secondarily prevent and to treat:

A. 1. Ischemic Heart diseases, e.g. Angina Pectoris and Myocard Infarcts;
   2. Cerebral vascular diseases in order to prevent Transient Ischemic attack (TIA) and Cerebrovascular accident (CVA);
   3. Intermittent Claudication;
   4. Ischemic Bowel disease; and
   5. Impotence due to a Periferal vascular disease.

B. Prevent excessive blood coagulation (high PAI-1 in the blood) in order to primarily prevent MI, CVA, Renal vein trombosis, etc.

C. Lower body weight (which is also a risk factor for high blood pressure, Glucose Intolerance, etc.)

Said dis ases are mainly caused, as indicated above, by a

high resistance to Insulin.

The present invention will now be illustrated with reference to the following experiment (all injections are given into the hollow space of the Peritoneum):

60 fat male rats of the Zucker species, aged 7 weeks having an average weight of 225 g. 54 rats of same are divided into 3 groups:

Group A receives injections of Octreotide in a 0.9% NaCl saline solution in a high dosage (40μg/kg/day);

Group B receives injections of Octreotide in a 0.9% NaCl saline solution in a low dosage (20 μg/kg/day); and

Group C the control group, receives an injection of a 0.9% saline solution. The volume of the 0.9% NaCl is identical with the volume being injected into Group A and B (At the beginning of the tests the rats have approximately the identical weight and they therefore receive the identical volume of injections).

All rats receive the same amount of Food (Pair Fed). Said amount is chosen according to the group eating the lowest amount. Thus, the influence of the drug is isolated.

The rats are located in a room changing light and darkness in order to simulate natural surroundings, as in general they eat in darkness. The rats drink water freely.

The rats are weighed twice a week. At the end of the experiment the rate change of the weight is being calculated. The amount of food eaten per week is measured and the amount eaten each day is calculated. (The influence of the Octreotide on the amount of food eaten by the rats is not checked. They eat the identical amount of food.)

Six rats are tested before the beginning of the experiment. Six rats from each group are separated after 2 weeks, 4 weeks and 8 weeks and an Intra-Peritoneal Glucose Tolerance Test (GTT 1.0g Glucose/kg BW) is performed after a fast of 12 hours during which the rats do not receive any medicament or food.

Blood is taken from the Supra-orbital sinus with slow anaesthesia with CO_2.

At zero time, i.e. before the Glucose load 2 cc of blood are taken from each rat.

½ cc of blood is put into a test tube which contains Heparin

and the concentrations of Glucose and Insulin are determined; and

1½ cc of blood is put into a test tube which contains Na_2EDTA 0.1% and the concentrations of Cholesterol, Triglycerides, HDL and LDL are determined.

At 15, 30 and 60 minutes after the Glucose load, ½ cc of blood is taken from each rat and put into a test tube which contains Heparin and the concentrations of Glucose and Insulin are determined.

After the Glucose tolerance test each tested rat "leaves" the experiment.

The materials used in the experiments:

Octreoide manufactured by Sandoz Basel.

0.9% NaCl

30% Glucose

Not sterilized food for mice and rats manufactured by Kopolk, Petach Tikva. Catalogue No. 19510. Gross energy 3,950 kCal/kg. Digestibality energy of the food in rats 3,150 kCal/kg.

The laboratory tests are performed as follows:

1. Glucose is tested by the Glucose Oxidase method in a kit of Boehringer Mannheim called Glucose GOD-Perid Method 2 x 300ml catalogue No. 124028. The test is performed on the day or the following day on which the blood is taken.

2. The Insulin is tested by the Radio Immuno Assay (RIA) by a SB INSIK-5 kit of Sorin Biomedica.

The method is performed by the general method known for the test of Insulin by said kit.

3. The total Cholesterol is tested by the CHOD-PAP method. The total cholesterol comprises VLDL + LDL + HDL. The kit with which the test is performed is manufactured by Boehringer Mannheim and the cholesterol reagent is MPA3 catalogue No. 236691 4 x 500ml.

The HDL is tested by precipitating LDL and VLDL with Heparin $MnCl_2$ and then the total cholesterol is tested. VLDL is calculated by T.G./5. LDL is calculated by the formula

LDL = totaL cholest rol - (VLDL + HDL)

4. The Triglycerides are being tested by the peridochrom T.G. GPO-PAP method. The kit is manufactured by Boehringer

Mannheim and the reagent has catalogue No. 701904 15 x 32ml.

The data received are worked up by standard methods for this purpose. The results show that the Insulin resistance is significantly lowered, there is an increase in the level of HDL and a decrease in the level of LDL and of the Triglycerides. A decrease in the rate of weight gain of young obese rats is observed, which implies a decrease in the weight of adult obese rats.

The Insulin resistance (Insulin Sensitivity Index) is determined using the dynamic test - the Glucose Tolerance Test (GTT). An integration of the area under the curve (AUC) of Glucose and Insulin in the period of 1½ hours is measured and the determination of the ratio between them gives a good estimate of the Insulin resistance.

Claims:

1. A pharmaceutical composition for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazideor one of its analogs(as herein defined) and metformin.
2. A pharmaceutical composition comprising an additional compound.
3. A pharmaceutical composition comprising an additional compound having an additional pharmaceutical effect.
4. A pharmaceutical composition according to Claim 2 or 3 wherein the additional compound is selected among carriers, solvents and emulgamators.
5. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Octreotide.
6. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Vapreotide.
7. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Lanreotide.
8. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs of somatostatin are Cyclopeptide somatostatin analogues selected among :

Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-δ-aminobutyric-Phe]
Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]
Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a)
Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]
Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser] (Ahep =(b)
Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]
Cyclo[Ahep-Phe-D-Trp-Lys-Thr]

Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]
Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)] (Ahex = (c)
Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)] (Aoct = (d)
Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]

(a) Bzl = benzyl
(b) Ahep = 7-aminoheptanoyl
(c) Ahex = 6-aminohexanoyl
(d) Aoct = 8-amino-octanoyl;

9. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol

10. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH_2 (Nal = (1)

11. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH_2

12. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH_2

13. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH_2 (Abu = (2)

14. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH_2

15. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH_2

16. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Ahep-Trp-D-Trp-Lys-Thr-Phe) (Ahep = (3)

17. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH_2 (Cpa = (4)

18. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH_2

19. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

20. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2

21. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH_2

22. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH_2

23. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH_2

24. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH_2

25. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH2

26. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are polypeptides of the formula:
X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y
wherein A is L- or D-Trp,
X is H-$(Aeg)_m$-Cys- or H-$(Aeg)_m$-Ala-Gly-Cys-,
Y is -Cys-$(Aeg)_n$-OH or
X and Y taken together are a 2-aminoethyl-glycyl group in the ring position and
m and n are 0, 1, 2, provided that
m and n are at least 1,
and their cyclic disulfide derivatives.

27. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH
3 4 5 6 7 8 9 10 11 12 13 14

in which

Bmp represents the desaminocysteine radical,

X represents Asn,

trp represents D-Trp that may be substituted in the benzene ring by a halogen atom, and

Y represents the radical of an alpha-(lower alkyl)amino-(lower alkyl)-carboxylic acid having a minimum of 4 and a maximum of 8 carbon atoms, in which the two lower alkyl radicals can be connected to one another with a single C-C bond, an oxygen atom or a sulphur (II) atom.

28. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are cyclic octapeptides of the formula

Asn-Phe-Phe-Trp-Lys-Thr-Phe-Gaba(Ar)
5 6 7 8 9 10 11 12

in which

Trp represents L-Trp or D-Trp, in which the benzene ring may be substituted by a fluorine atom, and

Gaba(Ar) represents the residue of a γ-aminobutyric acid substituted by a cyclic hydrocarbyl radical Ar selected from the group consisting of cyclohexyl; phenyl optionally substituted by halogen, nitro or phenoxy; and naphthyl optionally substituted by halogen.

29. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R_8
-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R_{18}-R_{19}-Phe-Phe-D
-Trp-Lys-Thr-R_{25}-R_{26}-R_{27}-R_{28}-OH wherein R_8 is

Met or Leu, R_{18} is Lys or des R_{18}, R_{19} is Asn or

des R_{19}, R_{25} is Phe or Tyr, R_{26} is Thr or des

R_{26}, R_{27} is Ser or D-Ser and R_{29} is D-Cys or Cys.

30. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R_8-Ala-Pro

-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R_{18}-R_{19}-Phe-Phe-D-Trp-Lys

-Thr-R_{25}-R_{26}-R_{27}-R_{28}-OH wherein R_8 is Met or

Leu, R_{18} is Lys or des R_{18}, R_{19} is Asn or des

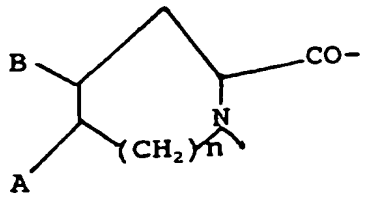
R_{19}, R_{25} is Phe or Tyr, R_{26} is Thr or des R_{26},

R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

31. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are cyclic hexapeptides of the formula

-X - Phe-D-Trp-Lys-Y-Phe-

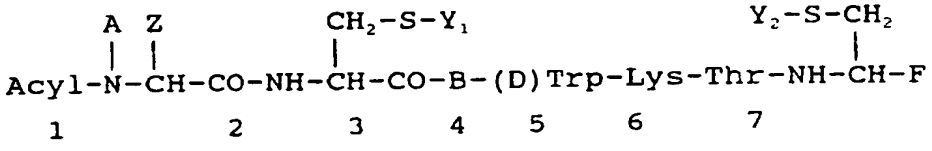
in which X represents the radical of an L-aminoacid of the formula



in which A and B are identical or different and denote alkyl having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms,
n denotes 0 or 1, and
Y represents an aliphatic or aromatic L-aminoacid the side-

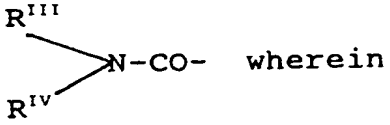
chair of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

32. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are N-acyl-polypeptides of formula,



wherein

"Acyl" is a group of formula $R^{I}CO-$ wherein R^{I} is C_{1-20} alkyl or phenyl; a group of formula $R^{II}SO_2-$ wherein R^{II} is C_{1-20}-alkyl, phenyl or tolyl; a group



wherein

R^{III} and R^{IV} are each independently hydrogen or C_{1-10}alkyl; or biotinyl,

A is hydrogen or C_{1-3}alkyl,

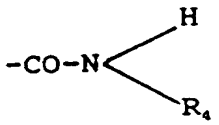
>N-CH(Z)-CO- is an (L)- or (D)-phenylalanine residue optionally ring-substituted by NO_2, or an (L) or (D)-norleucine residue,

whereby

Z in >N-CH(Z)-CO- represents the remainder of said residue,

B is -Phe- optionally ring-substituted by NO_2,

F is a group of formula



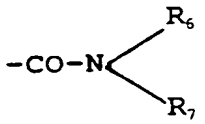
wherein R_4 is hydrogen or a group of formula

$-CH(R_5)-X$,

R_5 is $CH_3CH(OH)-$, i-butyl or benzyl

X is a group of formula $-COOR_1$,

$-CH_2OR_2$ or



wherein R_1, R_6 and R_7 are each hydrogen or C_{1-3}alkyl, and

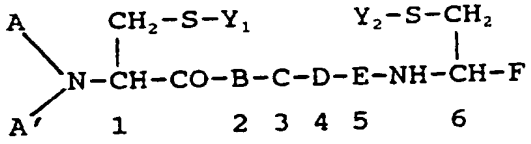
R_2 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

the group $-CH(R_5)-X$ having the (D)- or (L)-configuration, and

Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each indepen-dently have the (L)- or (D)-configuration, and with the proviso that:

i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only.

33. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are polypeptides of the formula



wherein

A is C_{1-12}alkyl, C_{7-10}phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C_{1-11}alkyl, phenyl or C_{7-10}phenylalkyl, or

ii) RCO- is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or C_{1-3}alkyl,

b) H-Asn-, or

c) H-Nle-Asn-,

the α-amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di-C_{1-12}alkylated,

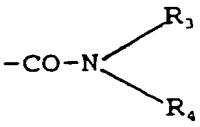
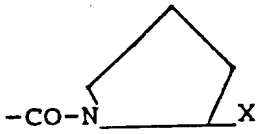
A' is hydrogen or, when A is C_{1-12}alkyl or C_{7-10}phenylalkyl, also C_{1-12}alkyl or C_{7-10}phenylalkyl,

B is -Phe-optionally ring-substituted by halogen and/or C_{1-3}alkyl,

C is -(L)- or -(D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen and/or C_{1-3}alkyl,

D is -Lys- optionally α-N-methylated and optionally Σ-N-C_{1-3}-alkylated,

E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally α-N-methylated,

F is a group of formula $-COOR_1$, $-CH_2OR_2$,  or 

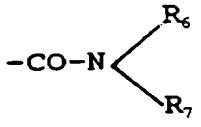
wherein R_1 is hydrogen or C_{1-3}alkyl,

R_2 is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R_3 is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}-phenylalkyl,

R_4 is hydrogen, C_{1-3}alkyl or, when R_3 is hydrogen or methyl, also a group of formula $-CH(R_5)-X$,

R_5 is hydrogen, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, $-CH_2-OH$, $-CH(CH_3)-OH$, isobutyl or benzyl

X is a group of formula $-COOR_1$, $-CH_2OR_2$ or 

wherein

R_1 and R_2 have the meanings given above,

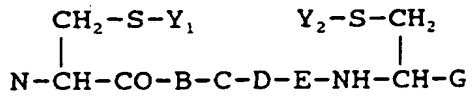
R_6 is hydrogen or C_{1-3}alkyl and

R_7 is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenylalkyl,

the group $-CH(R_5)-X$ having the D- or L- configuration, and Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

34. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is a compound of formula

A'



A

wherein

A is C_{1-12}alkyl, C_{7-10}phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C_{1-11}alkyl, phenyl or C_{7-10}phenylalkyl or

ii) RCO- is

a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, No_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy;

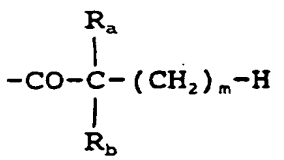
b) the residue of a natural or synthetic α-a-mino acid other than defined under a) above or of a corresponding D-amino acid, or

c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

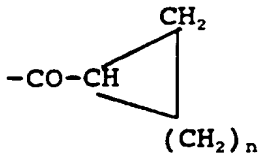
C_{1-8}alkanoyl,

A' is hydrogen,

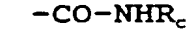
Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of formulae (1) to (5).



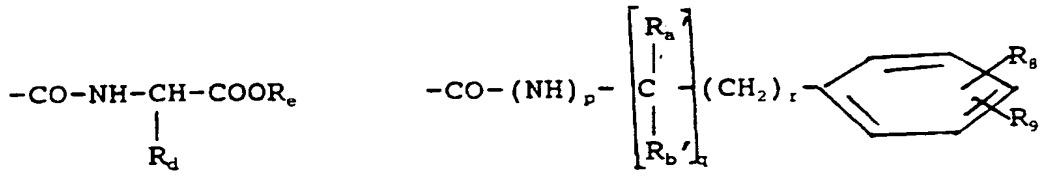
(1)



(2)



(3)

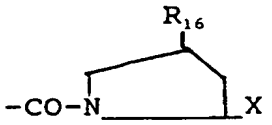


(4) (5)

wherein

R_a	is methyl or ethyl
R_b	is hydrogen, methyl or ethyl
m	is a whole number from 1 to 4
n	is a whole number from 1 to 5
R_c	is (C_{1-6})alkyl
R_d	represents the substituent attached to the α-carbon atom of a natural or synthetic α-amino acid (including hydrogen)
R_e	is (C_{1-5})alkyl
R_a' and R_b'	are independently hydrogen, methyl or ethyl,
R_8 and R_9	are independently hydrogen, halogen, (C_{1-3})alkyl or (C_{1-3})alkoxy,
P	is 0 or 1,
q	is 0 or 1, and
r	is 0, 1 or 2,
B	is -Phe- optionally ring-substituted by halogen, NO_2, NH_2, OH, C_{1-3}alkyl and/or C_{1-3}alkoxy (including pentafluoroalanine), or ß-naphthyl-Ala
C	is (L)-Trp- or (d)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, NO_2, NH_2 OH, C_{1-3}alkyl and/or C_{1-3} alkoxy,
D	is Lys, Lys in which the side chain contains O or S in ß-position, F-Lys or δF-Lys, optionally α-N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly residue
E	is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue
G	is a group of formula

$-COOR_7$, $-CH_2OR_{10}$, $-CON(R_{11})(R_{12})$ or



wherein

R_7 is hydrogen or C_{1-3}alkyl,

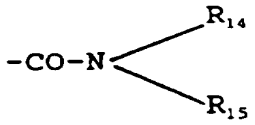
R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R_{11} is hydrogen, C_{1-9}alkyl, phenyl or C_{7-10}phenyl-alkyl,

R_{12} is hydrogen, C_{1-3}alkyl or a group of formula $-CH(R_{13})-X_1$,

R_{13} is CH_2OH, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, or $-CH(CH_3)OH$ or represents the substituent attached to the α-carbon atom of a natural or synthetic α-amino acid (including hydrogen) and

X_1 is a group of formula $-COOR_7$, $-CH_2OR_{10}$ or



wherein

R_7 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-3}alkyl and

R_{15} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenylalkyl, and

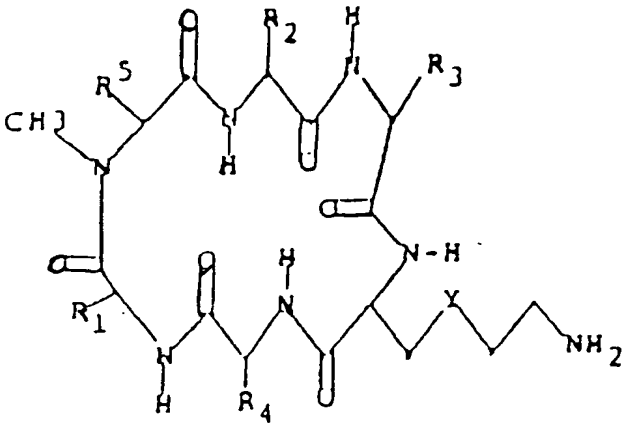
R_{16} is hydrogen or hydroxy,

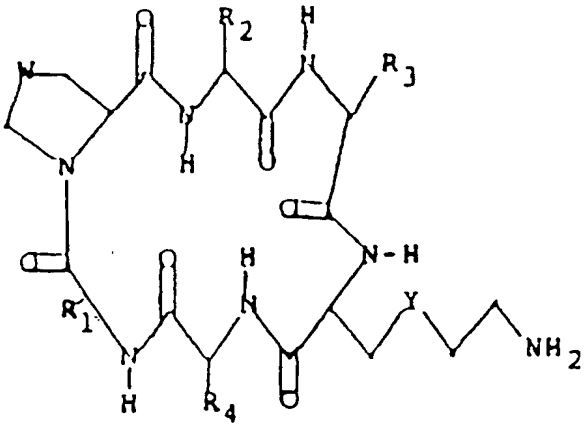
with the proviso that

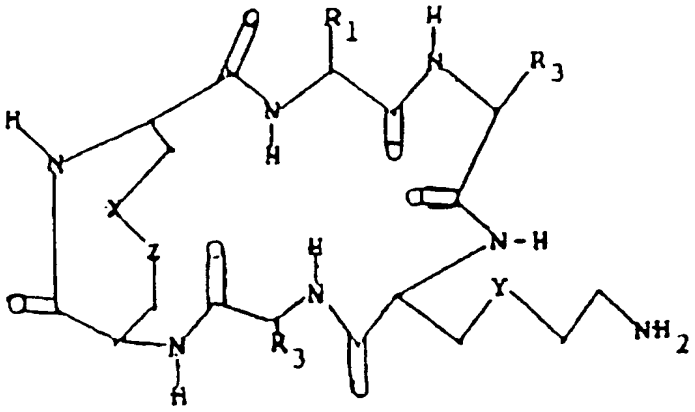
when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2-and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)- configuration.

35. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog is a somatostatin analog selected from the compounds of the following formulae



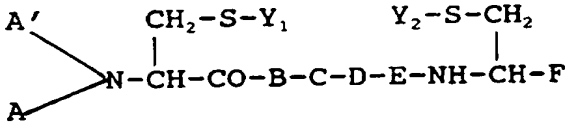




wherein

W is	S or $(CH_2)_s$ where s is 0, 1 or 2;
one of X and Z	is S and the other is S or CH_2;
Y is	S or $(CH_2)_t$ where t is 0, 1 or 2;
each of R_1 and R_2	independently of the other, is C_{1-5} alkyl, benzyl, benzyl having one or two C_{1-5} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-5} alkoxy substituents, or C_{1-5} alkyl substituted with 5- or 6-membered heterocyclic ring;
R_3 is	3-indolymethyl, either unsubstituted or having C_{1-5} alkyl, C_{1-5} alkoxy or halogen substitution;
R_4	C_{1-5} alkyl, C_{1-5} hydroxyalkyl, benzyl, carboxy-(C_{1-5} alkyl), amino (C_{1-5} alkyl) or benzyl having a C_{1-5} alkyl, halogen, hydroxy, amino, nitro and/or C_{1-5} alkoxy substituent;
R_5 is	C_{1-5} alkyl, benzyl, or benzyl having a C_{1-5} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-5} alkoxy substituent,

compounds of formula



wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula RCO-, whereby

i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl, or

ii) RCO-is

a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2, NH_2, OH, C_{1-3} alkyl and/or C_{1-3} alkoxy

b) the residue of a natural α-amino acid other than defined under a) above or of a corresponding D-amino acid, or

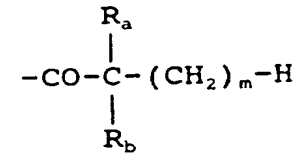
c) a dipeptide residue in which the individual amino acid

residues are the same or different and are selected from those defined under a) and/or b) above, the α-amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di-C_{1-12} alkylated,

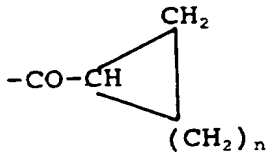
A' is hydrogen or, when A is C_{1-12} alkyl or C_{7-10} phenylalk- also C_{1-12} alkyl or C_{7-10} phenylalkyl,

Y_1 and Y_2 represent together a direct bond or

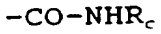
each of Y_1 and Y_2 is independently hydrogen or a radical of the formulae



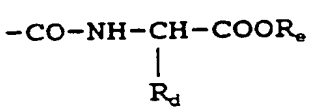
(1)



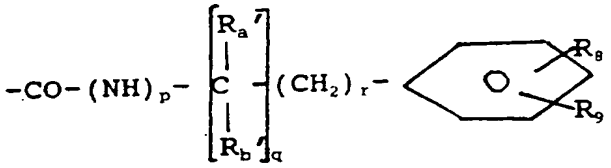
(2)



(3)



(4)



(5)

wherein R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is (C_{1-6})alkyl

R_d represents the substituent attached to the α-carbon atom of a natural α-amino acid (including hydrogen)

R_e is (C_{1-5})alkyl

R_a' and R_b' are independently hydrogen, methyl or ethyl,

R_8 and R_9 are independently hydrogen, halogen, (C_{1-3})alkyl or (C_{1-3})alkoxy,

p is 0 or 1,

q is 0 or 1, and

r is 0, 1 or 2,

B is -Phe- optionally ring-substituted by halogen, No_2, NH_2,

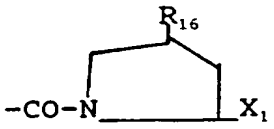
OH, C_{1-3}alkyl and/or C_{1-3}alkoxy, or naphthylalanine.

C is (L)-Trp- or (D)-Trp- optionally α-N-methylated and optionally benzene-ring-substituted by halogen, No_2, NH_2, OH, C_{1-3} alkyl and/or C_{1-3} alkoxy,

D is -Lys-, ThiaLys, F-Lys, δF-Lys or Orn, optionally α-N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,

E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue

F is a group of formula $-COOR_7$, $-CH_2OR_{10}$, $-CON(R_{11})(R_{12})$ or



wherein R_7 is hydrogen or C_{1-3}alkyl,

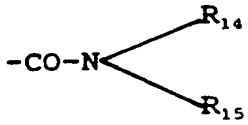
R_{10} is hydrogen or the residue of a physiologically acceptable,physiologically hydrolysable ester,

R_{11} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}-phenylalkyl,

R_{12} is hydrogen, C_{1-3}alkyl or a group of formula $-CH(R_{13})-X_1$,

R_{13} is CH_2OH, $-(CH_2)_2-OH$, $-(CH_2)_3-OH$, or $-CH(CH_3)OH$ or represents the substituent attached to the α-carbon atom of anatural α-amino acid (including hydrogen) and

X_1 is a group of formula $-COOR_7$, $-CH_2OR_{10}$ or



wherein

R_7 and R_{10} have the meanings given above,

R_{14} is hydrogen or C_{1-3}alkyl and

R_{15} is hydrogen, C_{1-3}alkyl, phenyl or C_{7-10}phenylalkyl, and

R_{16} is hydrogen or hydroxy,

with the proviso that

when R_{12} is $-CH(R_{13})-X_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)-configuration and compounds of the following formulae

H-Cys-Phe-(D)Trp-Lys-Thr-Phe-Cys-OH

-Asn-Phe-Phe-(D)Trp-Lys-Thr-Phe-Gaba-

-MeAla-Tyr-(D)Trp-Lys-Val-Ph

NMe-Phe-His-(D)Trp-Lys-Val-Ala.

36. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs are Somatostatin analogs

X-Cys-D-o-Trp-E-F-Cys-Y I

X-Cys-Lys-Asn-Phe-D-o-Trp-E-F-Phe-Thr-Ser-Cys-Y II

I,II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R^1); R^1 = C_{1-8}(fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH_2, NHR^1.

37. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides:
$RR^1NCHR^2CONHCH(CH_2SR^4)CO$-Phe-Trp-Lys-X-$NHCHR^3CH_2SR^5$
[R = inorg. or org. acyl group, R^1 = H, alkyl, $NCHR^2CO$ moiety = I.

$Me(CH_2)_8CO$-D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol I

or D-Phe (optionally ring substituted by halo, NO_2, OH, alkyl. alkoxy); Phe, Trp, (D or L) ,may be ring substituted by NO_2, NH_2, OH, alkyl, alkoxy; Lys may be α-N-methylated and Σ-N-alkylated; X = D- or L-α-amino acid residue optionally α-N-methylated; R^3 = CO_2H, CH_2OH, carbamoyl, R^4 = R^5 = H, R^4R^5

= bond]

38. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly

Cys-X^1-x^2-Phe-Phe-D-Trp-Lys-Tys-Thr-X^3-X^4-X^5-X^6-OH

39. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

40. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is
c(Spacer-Phe-D-Trp-Lys-Thr)
Spacer may stand for:
a) R,S-δ-Bn-o-AMPA
b) R-α-Bn-NMe-o-AMPA
c) Phe-Pro

41. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H_2N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

42. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
H_2N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

43. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatim analog is:
D-ß-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

44. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2

45. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH_2

46. A pharmaceutical composition according to any of Claims 1 to

4, wherein the somatostatin analog is:
D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH_2

47. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

48. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH_2

49. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH_2

50. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)
Aha = 7 -amino heptanoic acid.

51. A pharmaceutical composition according to any of Claims 1 to 4, wherein the active ingredient is diazoxide and comprises in addition a thiazide selected among chlorothiazide, hydrochlorothiazide, trichloromethiazide and polythiazide.

52. A method for the treatment of symptoms of syndrome X by applying to a patient a pharmaceutical composition according to any of Claims 1 to 51 comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazideor one of its analogs(as herein defined) and metformin.

53. A method according to Claim 52, wherein the pharmaceutically effective dosage (calculated on octreotide) does not exceed 50μ/kg/day.

54. A method according to Claim 53, wherein said dosage does not exceed 40μ/kg/day.

55. A method according to any of Claims 52 to 54 wherein the analog is Octreotide which is applied in the form of an injection in a 0.9% saline solution.

56. A method according to Claim 52, wherein said dosage does not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and does not exceed 15/mg/day in the treatment of children.

57. A method according to Claim 52, wherein the amount of metformin applied does not exceed 2.5 g/day divided into 2 - 3 portions.

58. Use of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs(as herein defined) and metformin in a preparation for the treatment of the risk factors of syndrome X of Reaven substantially as described in the specification.

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(74) Agent: DR. YITZHAK HESS & PARTNERS; P.O. Box 6451, 61063 Tel Aviv (IL).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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(54) Title: PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF SYNDROME X OF REAVEN

(57) Abstract

The present invention relates to a pharmaceutical composition comprising as active ingredient a compound selected among somatostatin or one of its analogs, diazoxide or one of its analogs, cyclothiazide or one of its analogs and metformin, for the treatment of syndrome X of Reaven (also called "Hyper Insulinemia syndrome" or "The Deadly Quartet").

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IL 97/00301

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/31 A61K31/54 A61K31/155

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHILLIPS R.E. ET AL: "Effectiveness of SMS 201-995, a synthetic, long-acting somatostatin analogue, in treatment of quinine-induced hyperinsulinaemia" LANCET THE, vol. 1, 1986, LONDON GB, pages 713-715, XP002053032 see the whole document ---	1-50, 52-55,58
X	BOYLE P.J. ET AL: "Octeotride reverses hyperinsulinaemia and prevents hypoglycemia induced by sulfonilurea overdoses" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 76, no. 3, 1993, pages 752-756, XP002053033 see the whole document ---	1-50, 52-55,58

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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2

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 1998	09.07.98

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CARRETTA, R. ET AL: "Reduction of blood pressure in obese hyperinsulinaemic hypertensive patients during somatostatin infusion" JOURNAL OF HYPERTENSION SUPPLEMENT, vol. 7, 1989, pages s196-s197, XP002053034 see the whole document ---	1-50, 52-55,58
X	KIRK, J.M.W. ET AL: "Somatostatin analogue in short term management of hyperinsulinism" ARCHIVES OF DISEASE IN CHILDHOOD, vol. 63, no. 12, 1988, page 14931494 XP002053035 see the whole document ---	1-50, 52-55,58
X	BLUMING A.Z. ET AL: "Successful treatment of unstable angina in malignant carcinoid syndrome using the long acting somatostatin analogue SMS 201-995 (sandostatin)" THE AMERICAN JOURNAL OF MEDICINE, vol. 85, 1988, pages 872-874, XP002053036 see the whole document ---	1-50, 52-55,58
X	US 4 100 153 A (GARSKY V.M.) 1978 see the whole document ---	1-50, 52-55,58
X	US 4 159 263 A (GARSKY VICTOR M) 26 June 1979 see the whole document ---	1-50, 52-55,58
X	EP 0 374 089 A (SANDOZ AG) 20 June 1990 see the whole document ---	1-50
A	RAYNOR K ET AL: "Cloned somatostatin receptors: identification of subtype-selective peptides and demostration of high affinity binding of linear peptides" MOLECULAR PHARMACOLOGY, vol. 43, no. 6, June 1993, pages 838-844, XP000676382 ---	1-50, 52-55,58
A	RAYNOR K ET AL: "Characterization of cloned somatostatin receptors SSTR4 and SSTR5" MOLECULAR PHARMACOLOGY, vol. 44, no. 2, August 1993, pages 385-392, XP000644418 see the whole document ---	1-50, 52-55,58

-/--

2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SIRTORI C.R. ET AL: "Re-evaluation of a biguanide, Metformin: mechanism of action and tolerability" PHARMACOLOGICAL RESEARCH, vol. 30, no. 3, 1994, pages 187-228, XP002053037 see the whole document ---	
A	SMITH U.: "Clinical and therapeutical aspects of the insulin resistance syndrome" CARDIOVASCULAR RISK FACTORS, vol. 3, no. 1, 1993, pages 67-73, XP002053038 see the whole document ---	
A	GUILLAUME G. ET AL: "Syndrome X et médecine générale" REVUE MEDICALE DE BRUXELLES, vol. 16, no. 2, 1995, XP002053039 see the whole document -----	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL 97/00301

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1(part.), 2-50 (comp.), 52(part.), 53-55(comp.), 58(part.)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1 (partially), 2-50 (completely), 52 (partially), 53-55 (completely), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising Somatostatin or one of its analogs; Uses of the said Somatostatin compositions.

2. Claims: 1 (partially), 51 (completely), 52 (partially), 56 (completely), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising diazoxide or one of its analogs; Uses of the said diazoxide compositions.

3. Claims: 1 (partially), 52 (partially), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising cyclothiazide or one of its analogs; Uses of the said cyclothiazide compositions

4. Claims: 1 (partially), 52(partially), 57 (completely), 58 (partially)

Pharmaceutical compositions for the treatment of the risk factors of syndrome X of Reaven comprising Metformin; uses of the said metformin compositions.

INTERN ONAL SEARCH REPORT

Information on patent family members

ıtio. ıpplication No
PCT/IL 97/00301

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